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(54) Title: HETEROCYCLIC DERIVATIVES AS ANTIDIABETIC AND ANTIOBESITY AGENTS

(57) Abstract

The instant invention is concerned with acetylphenols which are useful as antiobesity and antidiabetic compounds. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering or modulating triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for increasing gut motility or for treating atherosclerosis are also disclosed.

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HETEROCYCLIC DERIVATIVES AS ANTIDIABETIC AND ANTIOBESITY AGENTS

This application is a continuation-in part and claims priority to of each of the following U.S provisional applications: application no. 60/011080 filed February 2, 1996 (Merck attorney docket no. 19632PV); and application no. 60/----- filed December 23, 1996 (Merck attorney docket no. 19632PV2); each of which are herein incorporated by reference in their entirety.

This application is related to the following U.S. non-provisional applications: Serial No. --/----- filed January 31, 1997 (Merck attorney docket no. 19869Y) which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for microvascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy, hypertension, stroke, and heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

Type I diabetes (IDDM) is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II, noninsulin dependent diabetes mellitus (NIDDM) is due to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the main insulin-sensitive tissues, muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver.

The several treatments for NIDDM, which has not changed substantially in many years, are all with limitations. While physical

exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially high fat-containing food. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide, glipizide) which stimulate the pancreatic β–cells to secrete more insulin or by injection of insulin after the response to sulfonylureas fails, will result in high enough insulin concentrations to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from these last two treatments and increasing insulin resistance due to the even higher plasma insulin levels could theoretically occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea, respectively.

Thiazolidinediones (glitazones) are a recently disclosed class of compounds that are suggested to ameliorate many symptoms of NIDDM. These agents increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of NIDDM resulting in complete correction of the elevated plasma levels of glucose, triglycerides and nonesterified free fatty acids without any occurrence of hypoglycemia. However, serious undesirable effects have occurred in animal and/or human studies including cardiac hypertrophy, hemadilution and liver toxicity resulting in few glitazones progressing to advanced human trials.

Hyperlipidemia is a condition which is characterized by an abnormal increase in serum lipids, such as cholesterol, triglycerides and phospholipids. These lipids do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. See the *Merck Manual*, 16th Ed. 1992 (see for example pp. 1039-1040) and "Structure and Metabolism of Plasma Lipoproteins" in *Metabolic Basis of Inherited Disease*, 6th Ed. 1989, pp. 1129-1138. One form of hyperlipidemia is hypercholesterolemia, characterized by the existence of elevated LDL cholesterol levels. The

initial treatment for hypercholesterolemia is often to modify the diet to one low in fat and cholesterol, coupled with appropriate physical exercise, followed by drug therapy when LDL-lowering goals are not met by diet and exercise alone. LDL is commonly known as the "bad" cholesterol, while HDL is the "good" cholesterol. Although it is desirable to lower elevated levels of LDL cholesterol, it is also desirable to increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See, for example, Gordon, et al., Am. J. Med., *62*, 707-714 (1977); Stampfer, et al., N. England J. Med., *325*, 373-381 (1991); and Kannel, et al., Ann. Internal Med., *90*, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, but the quantities needed to achieve HDL raising are associated with undesirable effects, such as flushing.

It is suggested that thiazolidinedione compounds exert their effects by binding to the peroxisome proliferator activated receptor (PPAR) family of receptors, controlling certain transcription elements having to do with the biological entities listed above. See Hulin et al., Current Pharm. Design (1996) 2, 85-102. Three sub-types of PPARs have been discovered and described; they are PPARα, PPARγ and PPARδ. PPARα is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β–oxidation of fatty acids. PPARα is also involved with the activity of fibrates in rodents and humans. Fibric acid derivatives such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma triglycerides along with moderate reduction in LDL cholesterol, and they are used particularly for the treatment of hypertriglyceridemia.

The PPARγ receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. The DNA sequences for the PPARγ receptors are described in Elbrecht, et al., BBRC *224*;431-437 (1996). Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only

prostaglandin J_2 derivatives have been identified as natural ligands of the PPARγ subtype, which also binds thiazolidinedione antidiabetic agents with high affinity. The glitazones have been shown to bind exclusively to the PPARγ subtype.

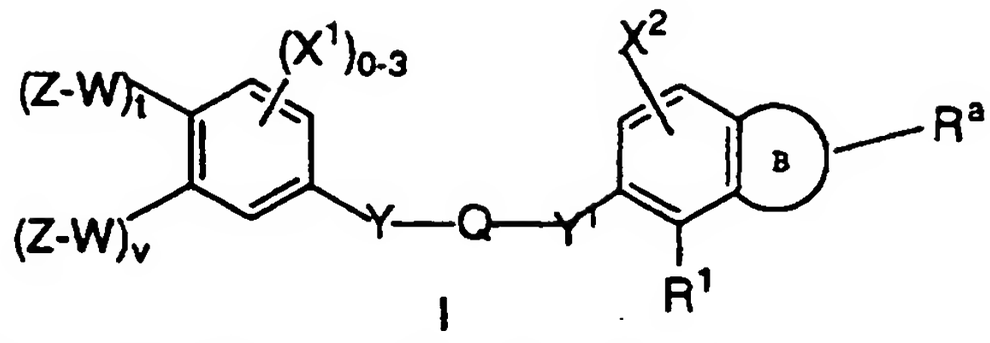
The human nuclear receptor gene PPARδ (hPPARδ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, *6* :1634-1641 (1992), herein incorporated by reference. It should be noted that PPARδ is also referred to in the literature as PPARβ and as NUC1, and each of these names refers to the same receptor; in Schmidt et al, the receptor is referred to as NUC1.

SUMMARY OF THE INVENTION

This invention is concerned with the compounds of formula I below and its analogs, pharmaceutically acceptable salts thereof, and bioprecursors thereof, which differ from the thiazolidinediones in that they lack the thiazolidinedione moiety and they do not lead to the array of toxicity's associated with the thiazolidinediones. The instant compounds are effective in treating diabetes, atherosclerosis, hyperglycemia, hyperlipidemia and/or obesity because they lower one or more of the following biological entities in mammals; glucose, insulin, triglycerides, fatty acids, cholesterol and the like. Thus, it is an object of this invention to describe such compounds. It is a further object to describe the specific preferred stereoisomers of the substituted compounds. A still further object is to describe processes for the preparation of such compounds. Another object is to describe methods and compositions which use the compounds as the active ingredient thereof. Further objects will become apparent from reading the following description.

DESCRIPTION OF THE INVENTION

The present invention is directed to a compound represented by formula I:



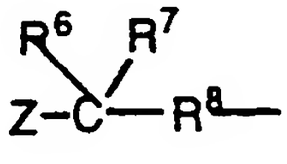
I

or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C1-6 alkyl, C5-10 aryl, and C5-10 heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^1 is selected from a group consisting of: H, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl and C3-10 cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R^3 is selected from a group consisting of: H, NHR^1, NHacyl, C1-15 alkyl, C3-10 cycloalkyl, C2-15 alkenyl, C1-15 alkoxy, CO2alkyl, OH, C2-15 alkynyl, C5-10 aryl, C5-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is $Z\text{-}CR^6R^7\text{-}$, Z-CH=CH-, or  ;

R^8 is selected from the group consisting of CR^6R^7, O, NR^6, and $S(O)_p$;

R^6 and R^7 are independently selected from the group consisting of H, $C_{1\text{-}6}$ alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the

five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3, $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, $=N(OR)$, SO_2R^3, NR^3R^3, NR^3COR^3, $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3, CO_2R^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3, $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t + v = 1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

Included in the invention is a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

Also included in the invention is a pharmaceutical composition which is comprised of a compound of formula I in combination with one or more known sulfonylureas, biguanides, α-glucosidase inhibitors, other insulin secretogogues as well as insulin.

Also included in the invention is a method for raising high densisty lipoprotein (HDL) plasma levels in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I.

Also included in the invention is a method for preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I.

Also included in the invention is a method for preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I in combination with one or more active agents such as antihyperlipidemic agents, HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and the like..

Also included in the invention is a method of treating or controlling diabetes, which comprises administering to a diabetic patient an effective amount of a compound of formula I.

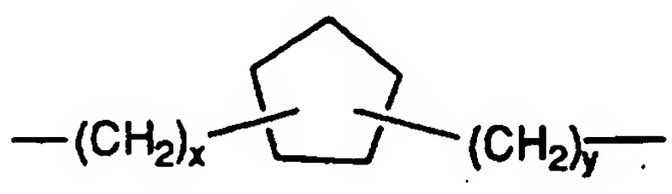
Also included in the invention is a method of treating or controlling diabetes, which comprises administering a compound of formula I in combination with one or more known sulfonylureas, biguanides, α-glucosidase inhibitors, other insulin secretogogues as well as insulin.

The invention is described herein in detail using the terms defined below unless otherwise specified.

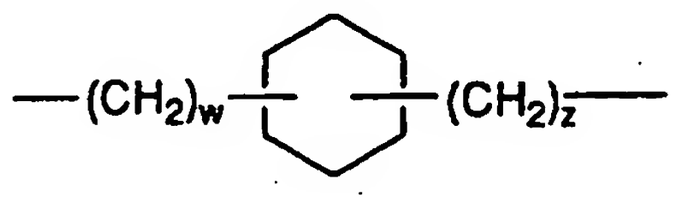
The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl,

propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

Alkyl also includes a straight or branched alkyl group which contains or is interrupted by a cycloalkylene portion. Examples include the following:



and



wherein: x and y = from 0-10; and w and z = from 0-9.

The alkylene and monovalent alkyl portion(s) of the alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain

triple bonds and may be substituted when a substituted alkynyl group is provided.

The term "alkoxy" refers to those groups of the designated carbon length in either a straight or branched configuration attached through an oxygen linkage and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

The term halo as used herein, represents fluoro, chloro, bromo or iodo.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 5 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted with 0-3 groups selected from R^a. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with zero or three groups of R^a.

Heteroaryl is a group containing from 5 to 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 0-3 R^a groups; examples of heteroaryls are pyridyl, quinolyl, purinyl, imidazolyl, imidazopyridyl and pyrimidinyl.

One embodiment of the novel compounds of the instant invention is realized when:

Y is O and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when:

Y is $S(O)_p$, p is 0-2 and all other variables are described as above.

Still another embodiment of the novel compounds of the instant invention is realized when:

Y is -CH_2- and all other variables are described as above.

Yet another embodiment of the novel compounds of the instant invention is realized when:

Y is CO and all other variables are described as above.

A further embodiment of the novel compounds of the instant invention is realized when:

Y is NR and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when:

Y is $NHSO_2$ or SO_2NH and all other variables are described as above.

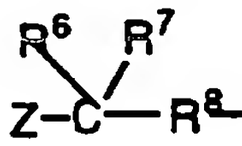
Another embodiment of the novel compounds of the instant invention is realized when:

Y is -C(O)NH- and all other variables are described as above.

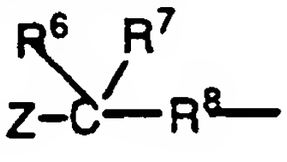
Another embodiment of the novel compounds of the instant invention is realized when:

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms G and J, which are substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when:

(Z-W-) is Z-CR^6R^7-, Z-CH=CH-, or  ; and all other variables are described as above and all other variables are described as above.

Still another embodiment of the novel compounds of the instant invention is realized when:

(Z-W-) is Z-CR^6R^7- or  ;

and all other variables are described as above and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when:Ra is selected from the group consisting of C1-6 alkyl, CF_3, aryl, halo, acyl, OCF_3, $-NO_2$, OR^3; COR^3, CO_2R^3, $CON(R^3)_2$, and $SO_2N(R^3)_2$; and X1 is selected from the group consisting of H, OH, C_{1-6} alkyl, C_{2-15} alkenyl, halo and OR^3 and all other variables are described as above.

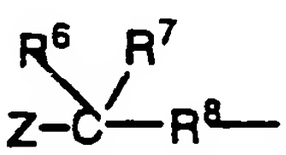
Another preferred embodiment of the novel compounds of the instant invention is realized when:
R is C_{1-6} alkyl or C_{5-10} aryl, said alkylor aryl optionally substituted with 1 to 3 groups of R^a;

R^1 is C_{1-15} alkyl;

X^1 & X^2 are independently H, C_{1-6} alkyl or halo;

Y is O, NH or S;

Y^1 is O;

(Z-W-) is Z-CR^6R^7- or  ;

R^a is a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, -O-, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, SO_2R^3, NR^3COR^3, COR^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl; and

Z is CO_2R^3, $CONHSO_2R$, $CONH_2$ or 5-(1H-tetrazole).

Examples of the compounds of the instant invention are:
Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy) propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazoloxy)-propylthio)phenyl acetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazole)oxy)propylthio phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy) propylthio)-phenylacetate;

3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio) phenyl-acetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate S-oxide;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid S-oxide;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy) propyl-thio)phenylacetate S,S-dioxide;

3-Chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazole)oxy)-propylthio phenylacetic acid S,S-dioxide;

tert-Butyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenyl acetate;

2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxy)propyl)thio)phenyl propionic acid;

Methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetic acid;

3-Chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxy) propylthio)phenylacetic acid;

Methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid;

3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxy)-butyloxy)phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenyl(2,2-dimethyl)acetic acid;

3-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenyl(2,2-dimethyl)acetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenyl(2,2-dimethyl)acetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenylpropan-3-oic acid;

4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butylamino)-phenylpropan-3-oic acid;

3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenoxyacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenoxyacetic acid;

4-(4-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)butyloxy)-phenoxyacetic acid;

N-[4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenyl]glycine;

N-[3-(4-(4-Phenyl-8-propylquinazolin-7-yloxy)butyloxy)-phenyl]glycine;

N-[4-(4-(4-Phenyl-8-propylquinazolin-7-yloxy)butyloxy)-phenyl]glycine;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenylacetic acid;

4-(3-(4-Phenyl-8-propylquinazolin-7-yloxy)propylthio)-phenylacetic acid;

3-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-phenylacetic acid;

3-(3-(2-Phenyl-5-propylbenzisoxazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

3-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(4-(3-Phenyl-7-prop-2-enylbenzisoxazol-6-yloxy)butyloxy)-3-chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenoxyacetic acid;

3-(3-(3-Phenyl-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-Phenyl-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-2-phenyl-2,2-dimethylacetic acid;

4-(4-(3-Phenyl-7-(cyclopropylmethyl)benzisoxazol-6-yloxy)butylamino)-phenoxy-2,2-dimethylacetic acid;

3-(3-(3-Neopentyl-7-propylbenzisoxazol-6-yloxy)propylthio)-3-methylphenylacetic acid

4-(3-(3-(2-Phenyl-2,2-dimethyl)-7-propylbenzisoxazol-6-yloxy)propyloxy)-3-butylphenylacetic acid;

4-(3-(3-Chloro-7-propylbenzisoxazol-6-yloxy)propylamino)-2-propylphenylacetic acid;

3-(3-(3-Chloro-7-propylbenzisoxazol-6-yloxy)propylamino)-2-propylphenylacetic acid;

4-(4-(3-Butoxy-7-propylbenzisoxazol-6-yloxy)butylthio)-2-fluorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenoxyacetic acid;

3-(3-(3-(3-Butylphenyl)-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-(2-Tolyl)-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-(4-Fluorophenyl)-7-propylbenzisoxazol-6-yloxy)propyloxy)-2-phenyl-2,2-dimethylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxy-2-*spiro*-cyclopropylacetic acid;

3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxy-2-*spiro*-cyclopropylacetic acid;

5-(4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)phenyl-2-(2,2-dimethyl)-ethyl)-tetrazole;

5-(4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)phenyl-3-propyl)-tetrazole;

5-(4-(4-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)butylamino)phenyl-3-propyl)-tetrazole;

5-(3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)phenoxy-2-ethyl)-tetrazole;

5-(4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)phenoxy-2-ethyl)-tetrazole;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-but-2-en-thio)phenylacetic acid;

4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid;

N-Methylsulfonyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5] isoxazole)oxy)propylthio phenyl acetamide;

3,5-dimethoxy-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenyl acetic acid;

3,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenyl acetic acid;

3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenyl acetic acid;

4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)-phenyl propionic acid;

3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid;

3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)-propylthio)phenylacetic acid;

2-methyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionic acid;

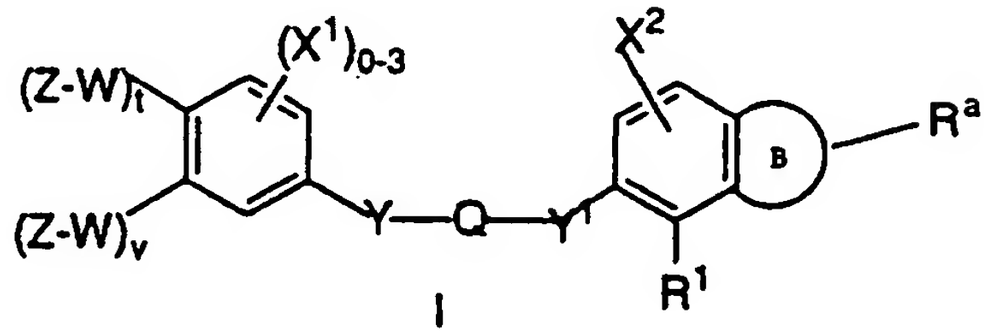
3-Propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

4-(3-(3-(Ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate;

3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazol-oxy)propylthio)phenylacetic acid;

WHAT IS CLAIMED IS:

1. A compound having the formula I:



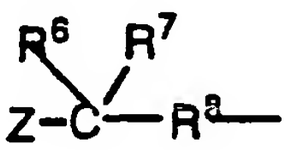
I

or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C_{1-6} alkyl, C_{5-10} aryl, and C_{5-10} heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^1 is selected from a group consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl and C_{3-10} cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R^3 is selected from a group consisting of: H, NHR^1, NHacyl, C_{1-15} alkyl, C_{3-10} cycloalkyl, C_{2-15} alkenyl, C_{1-15} alkoxy, CO_2alkyl, OH, C_{2-15} alkynyl, C_{5-10} aryl, C_{5-10} heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is $Z\text{-}CR^6R^7\text{-}$, Z-CH=CH-, or  ;

R^8 is selected from the group consisting of CR^6R^7, O, NR^6, and $S(O)_p$;

R^6 and R^7 are independently selected from the group consisting of H, C_{1-6} alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3, $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, $=N(OR)$, SO_2R^3, NR^3R^3, NR^3COR^3, $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3, CO_2R^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3, $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t + v = 1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

2. A compound of Claim 1 where X^1 & X^2 are independently H or halo.

3. A compound of Claim 1 where Y is O.

4. A compound of Claim 1 where Y is $S(O)_p$, wherein p is 0-2.

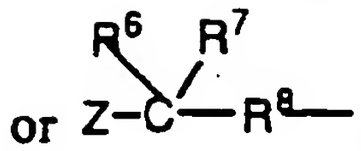
5. A compound of Claim 1 where Y is $-CH_2-$.

6. A compound of Claim 1 where Y is -CO-.

7. A compound of Claim 1 where Y is -NH-.

8. A compound of Claim 1 where Y is $-NHSO_2$ or $-SO_2NH$.

9. A compound of Claim 1 where Y is -C(O)NH-.

10. A compound of Claim 1 where (Z-W-) is $Z-CR^6R^7-$ or  ;

11. A compound of Claim 1 where B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a.

12. A compound of Claim 1 wherein:

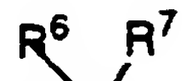
R is C_{1-6} alkyl or C_{5-10} aryl, said alkylor aryl optionally substituted with 1 to 3 groups of R^a

R^1 is C_{1-15} alkyl;

X^1 & X^2 are independently H, C1-6 alkyl or halo;

Y is O, NH or S;

Y^1 is O;

(Z-W-) is Z-CR^6R^7- or  ;

R^a is a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, SO_2R^3, NR^3COR^3, COR^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl; and

Z is CO_2R^3, $CONHSO_2R$, $CONH_2$ or 5-(1H-tetrazole).

13. A compound of Claim 1 selected from the group consisting of:
Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy) propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazoloxy)-propylthio)phenyl acetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazole)oxy)propylthio phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy) propylthio)-phenylacetate;

3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio) phenyl-acetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate S-oxide;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid S-oxide;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy) propyl-thio)phenylacetate S,S-dioxide;

3-Chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazole)oxy)-propylthio phenylacetic acid S,S-dioxide;

tert-Butyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenyl acetate;

2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxy)propyl)thio)phenyl propionic acid;

Methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetic acid;

3-Chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxy) propylthio)phenylacetic acid;

Methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid;

3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxy)-butyloxy)phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenyl(2,2-dimethyl)acetic acid;

3-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenyl(2,2-dimethyl)acetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenyl(2,2-dimethyl)acetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenylpropan-3-oic acid;

4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butylamino)-phenylpropan-3-oic acid;

3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenoxyacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenoxyacetic acid;

4-(4-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)butyloxy)-phenoxyacetic acid;

N-[4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenyl]glycine;

N-[3-(4-(4-Phenyl-8-propylquinazolin-7-yloxy)butyloxy)-phenyl]glycine;

N-[4-(4-(4-Phenyl-8-propylquinazolin-7-yloxy)butyloxy)-phenyl]glycine;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenylacetic acid;

4-(3-(4-Phenyl-8-propylquinazolin-7-yloxy)propylthio)-phenylacetic acid;

3-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-phenylacetic acid;

3-(3-(2-Phenyl-5-propylbenzisoxazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

3-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(4-(3-Phenyl-7-prop-2-enylbenzisoxazol-6-yloxy)butyloxy)-3-chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenoxyacetic acid;

3-(3-(3-Phenyl-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-Phenyl-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-2-phenyl-2,2-dimethylacetic acid;

4-(4-(3-Phenyl-7-(cyclopropylmethyl)benzisoxazol-6-yloxy)butylamino)-phenoxy-2,2-dimethylacetic acid;

3-(3-(3-Neopentyl-7-propylbenzisoxazol-6-yloxy)propylthio)-3-methylphenylacetic acid

4-(3-(3-(2-Phenyl-2,2-dimethyl)-7-propylbenzisoxazol-6-yloxy)propyloxy)-3-butylphenylacetic acid;

4-(3-(3-Chloro-7-propylbenzisoxazol-6-yloxy)propylamino)-2-propylphenylacetic acid;

3-(3-(3-Chloro-7-propylbenzisoxazol-6-yloxy)propylamino)-2-propylphenylacetic acid;

4-(4-(3-Butoxy-7-propylbenzisoxazol-6-yloxy)butylthio)-2-fluorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenoxyacetic acid;

3-(3-(3-(3-Butylphenyl)-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-(2-Tolyl)-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-(4-Fluorophenyl)-7-propylbenzisoxazol-6-yloxy)propyloxy)-2-phenyl-2,2-dimethylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxy-2-*spiro*-cyclopropylacetic acid;

3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxy-2-*spiro*-cyclopropylacetic acid;

5-(4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)phenyl-2-(2,2-dimethyl)-ethyl)-tetrazole;

5-(4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)phenyl-3-propyl)-tetrazole;

5-(4-(4-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)butylamino)phenyl-3-propyl)-tetrazole;

5-(3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)phenoxy-2-ethyl)-tetrazole;

5-(4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)phenoxy-2-ethyl)-tetrazole;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-but-2-en-thio)phenylacetic acid;

4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid;

N-Methylsulfonyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5] isoxazole)oxy)propylthio phenyl acetamide;

3,5-dimethoxy-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenyl acetic acid;

3,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenyl acetic acid;

3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenyl acetic acid;

4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)-phenyl propionic acid;

3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid;

3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)-propylthio)phenylacetic acid;

2-methyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionic acid;

3-Propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

4-(3-(3-(Ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate;

3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazol-oxy)propylthio)phenylacetic acid;

3-chloro-4-(3-(4-chlorophenylmethyl)-7-(n-propyl)-6-benz[4,5]isoxazol-oxy)propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl- N-methylamino)phenylacetate;

3,5-Dipropyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

3-fluoro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]isoxazoloxy)-propyloxy)phenylacetic acid;

3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)phenylacetic acid;

3-Isobutyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

3-Propyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy) propylthio)phenylacetic acid S,S-dioxide;

-Chloro-4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfoxy)phenylacetic acid;

3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)-butyloxy)phenylacetic acid;

3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)-propyl-thio)phenylacetic acid S, S-dioxide;

3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)-propyl-thio)phenylacetic acid S-oxide;

3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfinyl)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfonyl)) phenylacetic acid;

2,3-Dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

2-Trifloroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetic acid;

3-Chloro-4-(3-(3-cyclopropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)) phenylpropionic acid;

3-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)) phenylpropionic acid;

3-Chloro-4-(3-(3-(3-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenoxylacetic acid;

4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenylacetic acid;

3-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenylpropionic acid;

3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-benz[4,5]isox-azoloxy)propylthio)phenylacetic acid;

3-Methoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate;

3-(4-(2-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)ethyloxy)) phenylpropionic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenoxyacetic acid;

E-(4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy) cinnamic acid;

E-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy) cinnamic acid;

3-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy) phenylpropionic acid;

N-((4-carbomethoxymethyl)benzoyl)-3(3-phenyl-7-propyl-6-benz-[4,7]-isooxazolyloxy) propylamine ;

2-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)) phenoxypropionic acid;

2-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenoxypropionic acid;

3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetic acid;

1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio) phenyl cyclopropane carboxylic acid;

4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro-α, α–dimethyl-phenyl propionic acid;

3-Ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate; and

3-chloro-4-(3-(3-phenyl-6-propyl-5-benz-[4,7]-isoxazolyloxy)-propylthio) phenylacetic acid.

14. A compound of Claim 12 selected from the group consisting of:
Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy) propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazoloxy)-propylthio)phenyl acetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazole)oxy)propylthio phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy) propylthio)-phenylacetate;

3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio) phenyl-acetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate S-oxide;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid S-oxide;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy) propyl-thio)phenylacetate S,S-dioxide;

3-Chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazole)oxy)-propylthio phenylacetic acid S,S-dioxide;

tert-Butyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenyl acetate;

2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxy)propyl)thio)phenyl propionic acid;

Methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetic acid;

3-Chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxy) propylthio)phenylacetic acid;

Methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid;

3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxy)-butyloxy)phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propyloxy)-phenylacetic acid;

3-(4-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)butyloxy)-phenylacetic acid;

3-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butyloxy)-phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxyacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propyloxy)-phenoxyacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-3-propylphenylacetic acid;

4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butylthio)-3-chlorophenylacetic acid;

4-(4-(1-Phenyl-4-propylbenz[c]pyrazol-5-yloxy)butylthio)-3-chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylsulfono)-3-propylphenylacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylsulfono)-3-chlorophenylacetic acid;

4-(4-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)butylthio)-3-propylbenzyl-tetrazole;

4-(4-(3-Phenyl-7-propylindol-6-yloxy)butylthio)-3-chlorobenzyl-tetrazole;

4-(4-(1-Phenyl-4-propylindol-5-yloxy)butylthio)-3-chlorobenzyl-tetrazole;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenylacetic acid;

3-(4-(4-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)butyloxy)-phenylacetic acid;

3-(4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butyloxy)-phenylacetic acid;

3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)-propylthio)phenylacetic acid;

3-Propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

4-(3-(3-(Ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate;

3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazol-oxy)propylthio)phenylacetic acid;

3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)phenylacetic acid;

-Chloro-4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfoxy)phenylacetic acid;

3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)-butyloxy)phenylacetic acid;

3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfonyl)) phenylacetic acid;

2,3-Dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)) phenylpropionic acid;

3-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)) phenylpropionic acid;

3-Chloro-4-(3-(3-(3-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenylacetic acid;

3-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenylpropionic acid;

3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

3-(4-(2-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)ethyloxy)) phenylpropionic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenoxyacetic acid;

E-(4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy) cinnamic acid;

3-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy) phenylpropionic acid;

2-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)) phenoxypropionic acid;

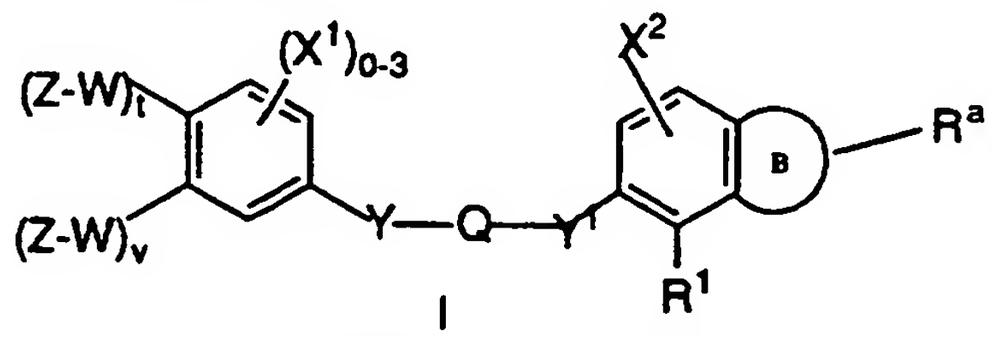
2-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenoxypropionic acid;

3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetic acid;

1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio) phenyl cyclopropane carboxylic acid; and

4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro-α, α–dimethyl-phenyl propionic acid.

15. A method for the treatment or prevention of diabetes which comprises administering to a diabetic patient an effective amount of a compound of formula I.



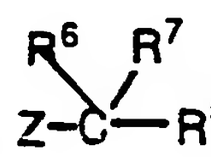
I

or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C_{1-6} alkyl, C_{5-10} aryl, and C_{5-10} heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^1 is selected from a group consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl and C_{3-10} cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R^3 is selected from a group consisting of: H, NHR^1, NHacyl, C_{1-15} alkyl, C_{3-10} cycloalkyl, C_{2-15} alkenyl, C_{1-15} alkoxy, CO_2alkyl, OH, C_{2-15} alkynyl, C_{5-10} aryl, C_{5-10} heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is $Z\text{-}CR^6R^7\text{-}$, Z-CH=CH-, or  ;

R^8 is selected from the group consisting of CR^6R^7, O, NR^6, and $S(O)_p$;

R^6 and R^7 are independently selected from the group consisting of H, C_{1-6} alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S; said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3, $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, $=N(OR)$, SO_2R^3, NR^3R^3, NR^3COR^3, $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3, CO_2R^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

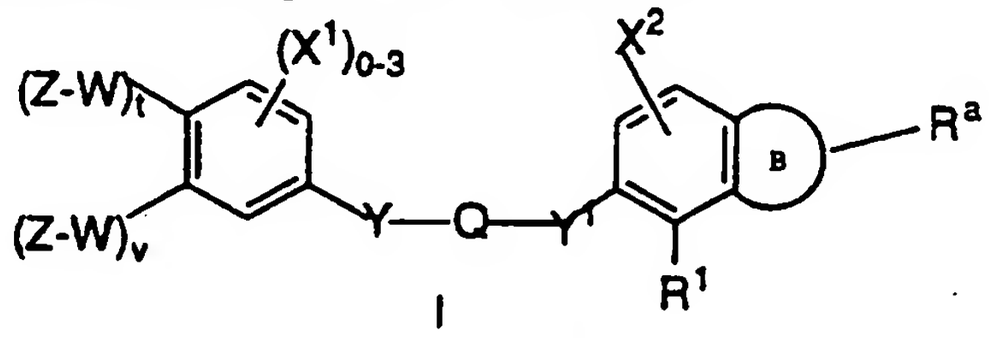
Z is selected from the group consisting of: CO_2R^3, $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t + v = 1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

16. A method for lowering triglyceride levels which comprises administering to a patient needing lower triglyceride levels an effective amount of a compound of formula I.



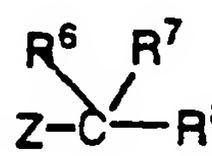
I

or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C_{1-6} alkyl, C_{5-10} aryl, and C_{5-10} heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^1 is selected from a group consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl and C_{3-10} cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R^3 is selected from a group consisting of: H, NHR^1, NHacyl, C_{1-15} alkyl, C_{3-10} cycloalkyl, C_{2-15} alkenyl, C_{1-15} alkoxy, CO_2alkyl, OH, C_{2-15} alkynyl, C_{5-10} aryl, C_{5-10} heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is $Z\text{-}CR^6R^7\text{-}$, Z-CH=CH-, or  ;

R^8 is selected from the group consisting of CR^6R^7, O, NR^6, and $S(O)_p$;

R^6 and R^7 are independently selected from the group consisting of H, C_{1-6} alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3, $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, $=N(OR)$, SO_2R^3, NR^3R^3, NR^3COR^3, $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3, CO_2R^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

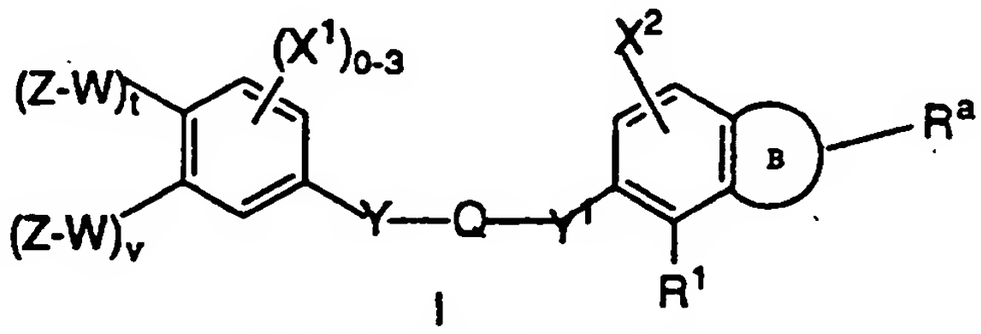
Z is selected from the group consisting of: CO_2R^3, $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t + v = 1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

17. A method for treating obesity which comprises administering to a patient in need thereof an effective amount of a compound of formula I.



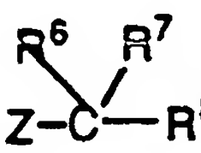
I

or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C_{1-6} alkyl, C_{5-10} aryl, and C_{5-10} heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^1 is selected from a group consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl and C_{3-10} cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R^3 is selected from a group consisting of: H, NHR^1, NHacyl, C_{1-15} alkyl, C_{3-10} cycloalkyl, C_{2-15} alkenyl, C_{1-15} alkoxy, CO_2alkyl, OH, C_{2-15} alkynyl, C_{5-10} aryl, C_{5-10} heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is $Z\text{-}CR^6R^7\text{-}$, Z-CH=CH-, or  ;

R^8 is selected from the group consisting of CR^6R^7, O, NR^6, and $S(O)_p$;

R^6 and R^7 are independently selected from the group consisting of H, C_{1-6} alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3, $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, $=N(OR)$, SO_2R^3, NR^3R^3, NR^3COR^3, $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3, CO_2R^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

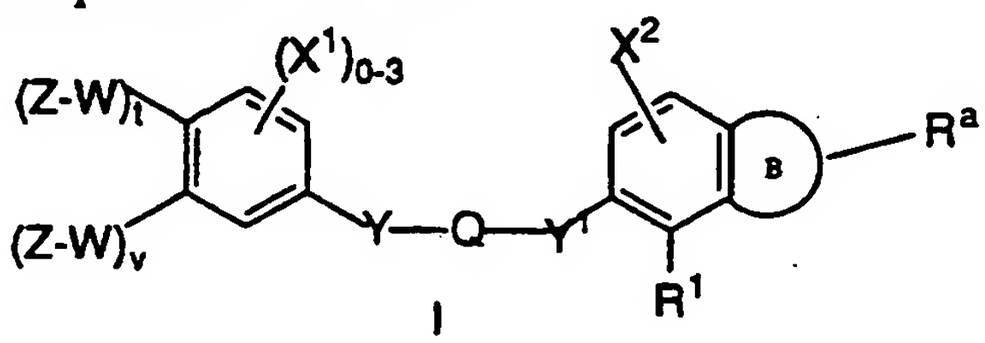
Z is selected from the group consisting of: CO_2R^3, $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t + v = 1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

18. A method for treating atherosclerosis or reducing the risk of developing atherosclerosis or having an atherosclerotic disease event comprising the administration to a mammal at risk of developing atherosclerosis or having an atherosclerotic disease event of an effective amount of a compound of formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C_{1-6} alkyl, C_{5-10} aryl, and C_{5-10} heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^1 is selected from a group consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl and C_{3-10} cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R^3 is selected from a group consisting of: H, NHR^1, NHacyl, C_{1-15} alkyl, C_{3-10} cycloalkyl, C_{2-15} alkenyl, C_{1-15} alkoxy, CO_2alkyl, OH, C_{2-15} alkynyl, C_{5-10} aryl, C_{5-10} heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is $Z\text{-}CR^6R^7\text{-}$, Z-CH=CH-, or  ;

R^8 is selected from the group consisting of CR^6R^7, O, NR^6, and $S(O)_p$;

R^6 and R^7 are independently selected from the group consisting of H, C_{1-6} alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3, $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, $=N(OR)$, SO_2R^3, NR^3R^3, NR^3COR^3, $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3, CO_2R^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3, $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t + v = 1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4

carbon atoms and

p is 0-2.

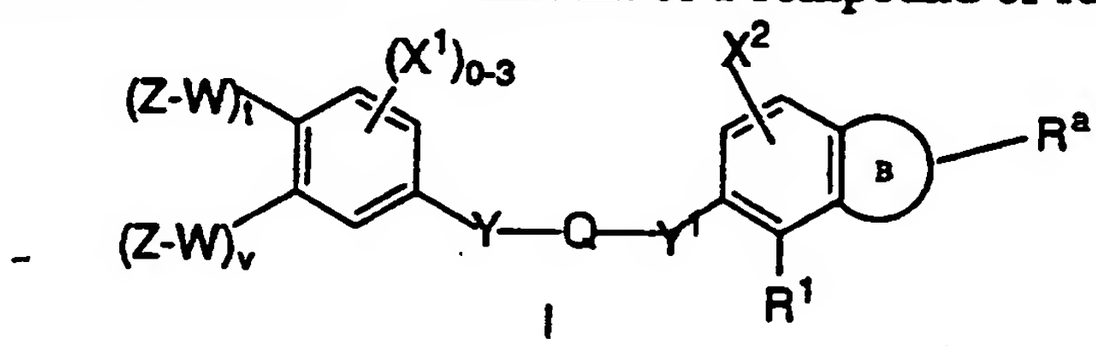
19. A method according to claim 18 wherein the compound has an IC_{50} equal to or less than 10 μM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 μM in the hPPARδ transactivation assay.

20. The method of Claim 19 wherein the compound has an IC_{50} equal to or less than 100 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 100 nM in the hPPARδ transactivation assay.

21. The method of Claim 20 wherein the compound has an IC_{50} equal to or less than 50 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 50 nM in the hPPARδ transactivation assay.

22. The method of Claim 21 wherein the compound has an IC_{50} equal to or less than 10 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 nM in the hPPARδ transactivation assay.

23. A method for raising high densisty lipoprotein plasma levels in a mamal in need of such treatment, comprising the administration of an effective amount of a compound of formula I.



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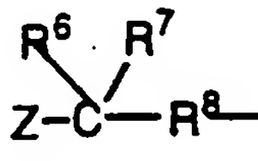
or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C_{1-6} alkyl, C_{5-10} aryl, and C_{5-10} heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^1 is selected from a group consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl and C_{3-10} cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R^3 is selected from a group consisting of: H, NHR^1, NHacyl, C_{1-15} alkyl, C_{3-10} cycloalkyl, C_{2-15} alkenyl, C_{1-15} alkoxy, CO_2alkyl, OH, C_{2-15} alkynyl, C_{5-10} aryl, C_{5-10} heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is Z-CR^6R^7-, Z-CH=CH-, or  ;

R^8 is selected from the group consisting of CR^6R^7, O, NR^6, and $S(O)_p$;

R^6 and R^7 are independently selected from the group consisting of H, C_{1-6} alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3, $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, $=N(OR)$, SO_2R^3, NR^3R^3, NR^3COR^3, $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3, CO_2R^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3, $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t + v = 1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

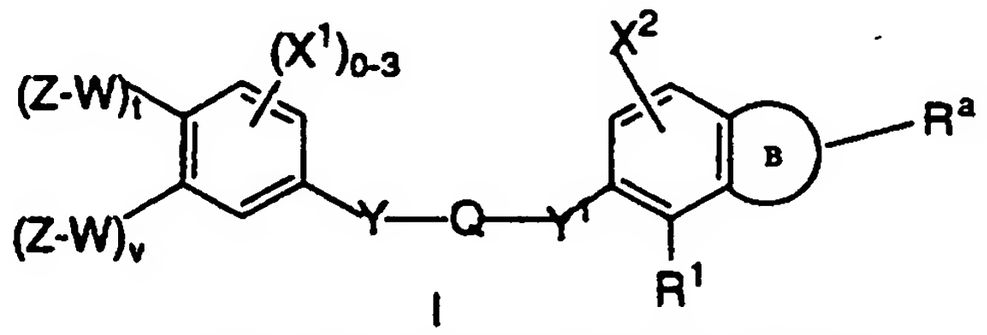
24. A method according to claim 23 wherein the compound has an IC_{50} equal to or less than 10 μM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 μM in the hPPARδ transactivation assay.

25. The method of Claim 24 wherein the compound has an IC_{50} equal to or less than 100 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 100 nM in the hPPARδ transactivation assay.

26. The method of Claim 25 wherein the compound has an IC_{50} equal to or less than 50 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 50 nM in the hPPARδ transactivation assay.

27. The method of Claim 26 wherein the compound has an IC_{50} equal to or less than 10 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 nM in the hPPARδ transactivation assay.

28. A post-myocardial infarction therapy comprising administering to a human who has suffered a myocardial infarction a compound of formula I.



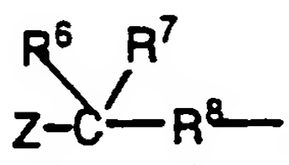
I

or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C_{1-6} alkyl, C_{5-10} aryl, and C_{5-10} heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^1 is selected from a group consisting of: H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl and C_{3-10} cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R^3 is selected from a group consisting of: H, NHR^1, NHacyl, C_{1-15} alkyl, C_{3-10} cycloalkyl, C_{2-15} alkenyl, C_{1-15} alkoxy, CO_2alkyl, OH, C_{2-15} alkynyl, C_{5-10} aryl, C_{5-10} heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is $Z\text{-}CR^6R^7\text{-}$, Z-CH=CH-, or 

;

R^8 is selected from the group consisting of CR^6R^7, O, NR^6, and $S(O)_p$;

R^6 and R^7 are independently selected from the group consisting of H, C_{1-6} alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3, $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3, OCF_3, CN, NO_2, R^3, OR^3; SR^3, $S(O)R^3$, $=N(OR)$, SO_2R^3, NR^3R^3, NR^3COR^3, $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3, CO_2R^3, $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3, $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t + v = 1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

29. A method according to claim 28 wherein the compound has an IC_{50} equal to or less than 10 μM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 μM in the hPPARδ transactivation assay.

30. The method of Claim 29 wherein the compound has an IC_{50} equal to or less than 100 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 100 nM in the hPPARδ transactivation assay.

31. The method of Claim 30 wherein the compound has an IC_{50} equal to or less than 50 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 50 nM in the hPPARδ transactivation assay.

32. The method of Claim 31 wherein the compound has an IC_{50} equal to or less than 10 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 nM in the hPPARδ transactivation assay.

33. A method for the treatment or prevention of diabetes which comprises administering to a diabetic patient an effective amount of a compound of Claim 15 in combination with a sulfonylurea, fibrate, HMG-CoA reductase inhibitor, beta-sitosterol inhibitor, cholesterol acyltransferase inhibitor, biguanides, cholestyramine, angiotensin II antagonist, melinamide, nicotinic acid, fibrinogen receptor antagonists, aspirin, α-glucosidase inhibitors, insulin secretogogue or insulin.

34. A method for halting, preventing or reducing the risk of developing atherosclerosis and related disease events which comprises administering to a patient in need thereof an effective amount of a compound of Claim 18 in combination with a sulfonylurea, fibrate, HMG-CoA reductase inhibitor, beta-sitosterol inhibitor, cholesterol acyltransferase inhibitor, biguanides, cholestyramine, angiotensin II antagonist, melinamide, nicotinic acid, fibrinogen receptor antagonists, aspirin, α-glucosidase inhibitors, insulin secretogogue or insulin.

35. A method according to claim 34 wherein the compound has an IC_{50} equal to or less than 10 μM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 μM in the hPPARδ transactivation assay.

36. The method of Claim 35 wherein the compound has an IC_{50} equal to or less than 100 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 100 nM in the hPPARδ transactivation assay.

37. The method of Claim 36 wherein the compound has an IC_{50} equal to or less than 50 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 50 nM in the hPPARδ transactivation assay.

38. The method of Claim 37 wherein the compound has an IC_{50} equal to or less than 10 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 nM in the hPPARδ transactivation assay.

39. A method for the treatment or prevention of obesity which comprises administering to an obese patient an effective amount of a compound of Claim 16 in combination with a fenfluramine, dexfenfluramine, phentiramine or β_3 adrenergic receptor agonist.

40. A composition for the treatment of diabetes or for lowering triglyceride levels or for halting, preventing or reducing the

risk of developing atherosclerosis and related disease events, or for raising high densisty lipoprotein plasma levels, which comprises an inert carrier and an effective amount of a compound of Claim 1.

41. A composition for the treatment of diabetes which comprises an inert carrier and an effective amount of a compound of Claim 1, in combination with a sulfonylurea, fibrate, HMG-CoA reductase inhibitor, beta-sitosterol inhibitor, cholesterol acyltransferase inhibitor, biguanides, cholestyramine, angiotensin II antagonist, melinamide, nicotinic acid, fibrinogen receptor antagonists, aspirin, α-glucosidase inhibitors, insulin secretogogue or insulin.

42. A composition for halting, preventing or reducing the risk of developing atherosclerosis and related diseae events, or for raising high density lipoprotein plasma levels,which comprises an inert carrier and an effective amount of a compound of Claim 1, in combination with a sulfonylurea, fibrate, HMG-CoA reductase inhibitor, beta-sitosterol inhibitor, cholesterol acyltransferase inhibitor, biguanides, cholestyramine, angiotensin II antagonist, melinamide, nicotinic acid, fibrinogen receptor antagonists, aspirin, α-glucosidase inhibitors, insulin secretogogue or insulin.

43. A method according to claim 42 wherein the compound has an IC_{50} equal to or less than 10 μM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 μM in the hPPARδ transactivation assay.

44. The method of Claim 43 wherein the compound has an IC_{50} equal to or less than 100 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 100 nM in the hPPARδ transactivation assay.

45. The method of Claim 44 wherein the compound has an IC_{50} equal to or less than 50 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 50 nM in the hPPARδ transactivation assay.

46. The method of Claim 45 wherein the compound has an IC_{50} equal to or less than 10 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 nM in the hPPARδ transactivation assay.

47. A composition for the treatment of obesity which comprises an inert carrier and an effective amount of a compound of Claim 1, in combination with a fenfluramine, dexfenfluramine, phentiramine or β_3 adrenergic receptor agonist.

INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/US 97/01749

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D261/20 C07D275/04 A61K31/42 A61K31/425 C07D263/56
C07D231/56 C07D249/18 C07D239/74 A61K31/505 A61K31/415
A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 611 003 A (MERCK & CO INC) 17 August 1994 see claims -----	1,15-47

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 April 1997	21.04.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US 97/01749

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Athough claims 15-47 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. nal Application No
PCT/US 97/01749

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0611003 A	17-08-94	US 5451677 A	19-09-95
		AU 670477 B	18-07-96
		AU 5498694 A	29-06-95
		CA 2114712 A	10-08-94
		JP 7010827 A	13-01-95
		WO 9418161 A	18-08-94
		ZA 9400846 A	05-09-94